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09/467,076    12/20/99    CIBELLI    J    000270-088

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HM12/1002

EXAMINER

WOITACH, J

ART UNIT

PAPER NUMBER

1632

DATE MAILED:

10/02/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

Application No.

09/467,076

Applicant(s)

CIBELLI ET AL.

Examiner

Joseph Voitach

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 04 May 2000.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-54 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-54 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

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#### DETAILED ACTION

This application filed December 20, 1999 which claims benefit to PCT/US99/04608, filed March 2, 1999, which claims priority to 08/699,040, filed August 19, 1996, and is a continuation in part of 09/395,368, filed September 14, 1999, now abandoned, which is a continuation in part of 09/260,468, filed March 2, 1999, which are a continuation in part of 09/032,945, filed March 2, 1998, now abandoned, which is a continuation in part of 08/699,040, filed August 19, 1996.

Applicants pre-amendment filed May 4, 2000, paper number 6, has been received and entered. The specification has been amended. Claims 1-54 are pending and currently under examination.

#### *Oath/Declaration*

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It was not executed in accordance with either 37 CFR 1.66 or 1.68. Robert Lanza failed to date his signature on page 3.

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### *Specification*

The specification is objected to because the reference to related applications should be updated to reflect the status of the applications. On page 20 of the specification, the recitation of 'karyoplast?????' is unclear. Correction is required. See MPEP § 608.01(b).

In addition, on page 15, a brief description of the figures is included for five figures, however, no figures have been submitted. Clarification is required. Further, if figures are supplied, a figure legend with a description for each figure must be present in the specification. Correction may be required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27-32 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to 'embryonic or stem-like cells' and 'human embryonic or stem-like cells'. As written, the claims read on cells that are a human embryo. A human being or human embryo is not-statutory subject matter. See 1077 O.G. 24, April 21, 1987.

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***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-54 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for the production of human or mammalian embryonic or stem-like cells comprising; inserting a differentiated human or mammalian cell or nucleus into an enucleated oocyte from a different animal species than the human or mammalian cell forming a NT unit; activating the NT unit; inserting cytoplasm into the oocyte from the same species of animal as the donor cell or nucleus; culturing the activated NT unit into cells; and culturing the cells to obtain embryonic or stem-like cells. Further, embodiments include, differentiating or genetically modifying the resulting embryonic or stem-like cells. The claimed invention is further directed to the products produced by said methods. The specification discloses the preparation of nuclear transfer units using a method of nuclear transfer of adult human epithelial cell nuclei into enucleated bovine oocyte to form a nuclear transfer (NT) unit by electrofusion techniques. The method disclosed in Example 1 of the specification result in the production of a NT unit (16-400 cell stage) according to Table 1, page 64. Although the methods of the instant invention result in the production of a NT unit of which Applicants report propagates into what appears to be

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ES-like cell colonies (as determined by cell morphology); Applicants fail to demonstrate that the ES-like cells function as true ES-cells in that they are in fact totipotent or that they function as stem cells in that they are capable of differentiation into other multilineage cell-types. As such, Applicants fail to enable the production of embryonic or stem-like cells as recited in step (v).

The unpredictability of the method of NT transfer, as a whole, lies in the need to convert a differentiated cell to a totipotent cell (embryonic stem cell). Cells contain the same DNA complement, however, in differentiated tissues, not all DNA sequences are expressed. For example, a liver does not make rhodopsin and retinal cell structures, and retinal cells do not make clotting factors and hepatocyte structures. For a cell to go through all the steps of development, it, or its nucleus, must be reverted to the stage where all DNA sequences can potentially be expressed, and expression regulated according to developmental stage. Applicants have not provided evidence that the cells produced by their methods are true pluripotent cells (embryonic stem cells or embryonic or stem-like cells). Applicants fail to demonstrate whether their ES-like cells stain positive for alkaline phosphatase (AP), exhibit the formation of embryoid bodies, spontaneously differentiate into at least two different cell type, or express ES cell markers. Applicants only disclose several morphological characteristics (Example I, page 62). Further,, it is to predictable (without specific guidance) whether Applicants' ES-like cells are even cells which are capable of differentiation upon induction to a particular cellular pathway, e.g., lineage or multilineage precursor. Applicants acknowledge that the prior art is lacking in the production of inner cell mass cells from NT units useful to form ES cell-like colonies that could

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be propagated (page 7, lines 10-13). Thus, the skilled artisan would not have found guidance from the art on the methodology of nuclear transfer utilizing differentiated adult human or mammalian cells or nuclei for insertion into bovine enucleated oocytes. For this, the artisan could only rely on the instant specification and in light of the very low frequency of NT units produced by the method, the lack of a showing demonstrating differentiation from the produced cells, and the lack of evidence demonstrating ES cell totipotency; the claimed invention is not enabled by the specification. As such, as the specification discusses "how to use" cells obtained from the NT process for production of differentiated cells useful for cellular transplantation, it is unknown how the skilled artisan would be able "to use" the claimed cells (embryonic or stem-like cells) in a manner which is consistent with the specification without specific guidance.

Applicants rely on prior art methods for induction of differentiation using their resulting embryonic or stem-like cells. However, differentiation of ES cells is species-dependent. This observation is supported by Stice *et al.* (Theriogenology, 1998) who disclose that "[o]verall, an obvious conclusion of mammalian nuclear transfer studies is that the results obtained often depend on species investigate in the study (see page 130, first paragraph in the Species Specific Difference). Further, Stice *et al.* discuss that the degree of differentiation depends on the source of terminally differentiated nuclei as well as other factors (paragraph bridging pages 131-132). Thus, it is inappropriate to rely on the prior art with respect to mouse (or any other species) ES cell differentiation techniques as it applies to the embryonic or stem-like cells of the instant invention. It is also not clear from the specification what contribution (functionally or

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structurally), if any, the bovine cytoplasm (or mitochondria) makes to the resulting embryonic or stem-like cell of the instant invention. Further, in view of structural (or functional) differences in the ES-like cells of the instant invention, the skilled artisan would not reasonably expect to induce differentiation into other cell lineages using techniques in the art available for mouse ES cells. As such, the specification fails to provide guidance and direction for critical parameters of the claimed invention with respect to obtaining true totipotent embryonic stem cells which give rise to germline tissue and the whole animal, or even embryonic cells which are merely capable of differentiation, for example. Note that the claim limitation "embryonic or stem-like cell" is vague and indefinite and clearly encompasses and reads on a cell which is an embryonic stem cell as known in the art or is a progenitor cell which appears similar morphologically but is only capable of differentiation. See the following rejection under 112, second paragraph, with respect to this claim limitation.

Further, with regard to the structure and function of the cells produced by the NT methods of the invention, Dominko *et al.* (Biology of Reproduction, 1999) support that cross-species NT cannot be judged as useful before nuclear reprogramming, somatic cell/recipient cytoplasm compatibilities are examined (see page 1501, last paragraph). With regard to examining nuclear reprogramming or dedifferentiation, Dominko *et al.* disclose that such can only be determined by demonstration of a pregnancy carried to term. As Dominko *et al.* only teach that bovine cytoplasm has the ability to support several mitotic cell cycles directed by newly introduced nuclear DNA, importantly, they note that "(whether this introduced differentiated DNA is

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reprogrammed, is modified, or simply remains unchanged is currently under investigation." (see page 1501, first column, first paragraph). As such, in view of the supported undeveloped and unpredictable state of the art with respect to the characterization of cells produced by cross-species NT, Applicants' demonstration of the production of only one NT unit (Table 1) cannot be extrapolated to the production of embryonic stem cells as known in the art or as precursor cells as known in the art.

The courts have stated that:

a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies Inc.* R02 F M 1367, 1385,231 USPQ81, 94(Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.** *Genentech Inc. v. Novo Nordisk A/S* 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

In the instant case, the specification fails to provide guidance to the skilled artisan on any parameters which would be necessary and critical for the production of human or mammalian embryonic or stem-like cells by the cross-species NT process which exhibit embryonic stem cell properties or even mere differentiation upon induction.

Furthermore, the specification in particular has not provided a use for human embryonic stem (ES) cells made by the method in that such cells, if true ES cells, have the potential upon transfer

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to a host to develop into a human being. As certain of the product claims recite "human embryonic or stem-like cells", this argument is proper in that the term "embryonic stem cell" has a well known potential in the art to give rise to the corresponding species of animal. It is acknowledged that Applicants contemplate the production of human stem cell multilineage precursors, however, since Applicants also discuss the ES cell potential for germ-line manipulation (pages 2-6) with respect to ES cells of non-human mammalian species, it is not clear how and under what circumstances, humans would be so made from the ES-like cells of the invention. If Applicants do not intend for use of the cells of the invention in such a manner, Applicants may wish to choose different claim terminology better describing the cells of the invention.

It is noted that it appears that the state of the art, as it specifically pertains to the instant application and claimed invention, is clearly lacking in supported evidence. In particular, Marshall (PNAS, 1998) discloses that "Robl concedes that the experiment did not yield publishable data" and that [Robl] "classified the cells as human stem cells based on his experience of looking at hundreds and hundreds of cell colonies." Marshall discloses, that at that time, none of the normal tests had been performed to demonstrate that these cells were human or that they were stem cells. Furthermore, Marshall reports that one skilled in the art, had stated that the cells in question had met none of the criteria for embryonic stem cells. As such, it would have required undue experimentation for one skilled in the art to perform the claimed methods of NT transfer for production of cells which meet the criteria of a true embryonic stem cell, or rather a stem cell of

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sort, which upon differentiation, would provide cellular or gene therapy upon transplantation. Applicants must provide a nexus between the production of their one NT unit and claims directed to "embryonic or stem-like cells" and claims directed to using differentiated cells for cellular transplantation and gene therapy.

With regard to claims 36-54, the specification fails to teach the gene modification of any differentiated cell produced by their methods, and in fact, fails to perform differentiation assays using the produced NT unit. The specification additionally fails to teach the use of gene-modified differentiated cells as a starting point in the method of cross-species nuclear transfer. As such, the specification fails to enable the gene-modification of cells for use in the methods or as produced by the methods.

Therefore, in view of art of record it would have required undue experimentation to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the absence of working examples for the demonstration of or reasonable correlation to producing human or mammalian embryonic or stem-like cells capable of mere differentiation, for example, the unpredictability and undeveloped state to the art with respect to cross species nuclear transfer (using adult differentiated nuclei) for production of embryonic stem cells which give rise to germline tissue and the whole animal or which may be induced to differentiate, in particular with respect to carrying out a process involving insertion of differentiated, adult human cell nuclei into bovine oocytes, the unpredictable state of the art with respect to extrapolating

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results obtained from ES cells of different species of animals to results obtained from chimeric bovine/human embryonic or stem-like cells.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

In claims 1, 24-32 and 38, the recitation of "embryonic or stem-like cells" is vague and indefinite with respect to structure and function of the cells. For example, do Applicants intend to claim embryonic stem cells, stem cell progenitors or precursor cells, or both? Applicants refer to the term "stem cell-like" with respect to the contribution of the bovine oocyte mitochondria, however, does such a structural contribution have any effect on the function of an embryonic stem cell, such that the resulting cells can not be termed embryonic stem cells? If the contribution of bovine mitochondria has absolutely no effect on the function of the resulting and/or

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amendment to the claims is requested. Dependent claims are included in this rejection because they fail to clarify the basis of the rejection.

Claim 1 is unclear in the recitation of ("compatible cytoplasm") because the relationship of this phrase to the rest of the claim is not clearly defined. In addition, this phrase is not used in any dependent claim so it is not clear why this term is introduced into the claim. Dependent claims are included in this rejection because they fail to clarify the basis of the rejection.

Claim 1 is unclear in the recitation of ("compatible mitochondria") because the relationship of this phrase to the rest of the claim is not clearly defined. In addition, this phrase is not used in any dependent claim so it is not clear why this term is introduced into the claim. Dependent claims are included in this rejection because they fail to clarify the basis of the rejection.

Claim 35 recites the limitation "which contain and express an inserted gene" and there is insufficient antecedent basis for this limitation in the claim. The claim depends from a claim directed to cells obtained by a method which does not involve gene modification. Amendment to the claim is required. Dependent claims are included in this rejection because they fail to clarify the basis of the rejection.

Claim 36 recites the limitation "wherein a desired gene is inserted, removed or modified" and there is insufficient antecedent basis for this limitation in the claim. The claim depends from a method which does not involve gene modification. Amendment

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to the claim is required. Dependent claims are included in this rejection because they fail to clarify the basis of the rejection.

Claim 50 is vague and indefinite in the recitation "a DNA that encodes to a detectable marker, the expression of which is linked to a particular cyclin." In light of the specification it is unclear what type of marker is encompassed by the claim, can the mRNA of a particular cyclin be considered a marker? It is unclear if the claim is drawn to a fusion protein or the "particular cyclin" is a promoter sequence which controls expression of the detectable marker. Further, in light of the specification it is unclear what type of marker is encompassed by the claim, can the mRNA of a particular cyclin be considered a marker? Clarification and/or amendment to the claim is requested. Dependent claims are included in this rejection because they fail to clarify the basis of the rejection.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 27 is rejected under 35 U.S.C. 102(b) as being anticipated by Bradley et al. (Biotechnology, 1992).

Claim 27 is directed to embryonic or stem-like cells. It should be noted that the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). This is because the final product (the embryonic or stem-like cells) is not distinguished by any particular features or characteristics as a result of the process by which it is made. As such, the limitations of the claimed cells are met by any embryonic or stem-like cell in the prior art. As such, note that it is not clear as to what the phrase "embryonic or stem-like cells" encompasses. See rejection under 35 U.S.C. 112, second paragraph. Thus, in the instant rejection, the phrase is being interpreted as embryonic stem cells. Bradley *et al.* teach mouse embryonic stem cell lines ABI, AB2.1, and CCE, which display germline transmission.

Accordingly, Bradley *et al.* clearly anticipate claim 18.

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Claims 27-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Granerus *et al.* (Cell Proliferation, 1996).

The claims are directed to human embryonic or stem-like cells. Note that it is only the product which is anticipated by the prior art and not the process by which the product is made. This is because the final product is not distinguished by any particular features or characteristics as a result of the process by which it is made. As such, the limitations of the claimed cells are met by any embryonic or stem-like cell in the prior art. As such, note that it is not clear as to what the phrase "human embryonic or stem-like cells" encompasses. See rejection under 35 U.S.C. 112, second paragraph. Thus, in the instant rejection, the phrase is being interpreted as cells which exhibit similar properties as that of human embryonic stem cells. Granerus *et al.* disclose a human cell line, Tera 2, which functions in several aspects as a human embryonic stem cell (see summary in abstract). Thus, without a distinguishing structural or functional difference of the claimed cells, the human cells of Granerus *et al.* having embryonic stem cell activity meet all of the limitations of the claimed cells.

Accordingly, Graneus *et al.* clearly anticipate claims 18-23.

Claims 27-34 and 50-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Tsukamoto *et al.* (US Patent 5,716,827).

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The claims are directed to human embryonic or stem-like cells. Claims 50-54 are drawn to a mammalian somatic cell that expresses DNA that encodes a detectable marker linked to a particular cyclin. As noted in the 35 USC 112, second paragraph, rejection, the mRNA of the cyclin itself could serve as a marker, and thus, absent a means of detection, any cell containing and expressing a cyclin would anticipate the claim. Note that it is only the product which is anticipated by the prior art and not the process by which the product is made. This is because the final product is not distinguished by any particular features or characteristics as a result of the process by which it is made. As such, the limitations of the claimed cells are met by any embryonic or stem-like cell in the prior art, and note that it is not clear as to what the phrase "human embryonic or stem-like cells" encompasses. See rejection under 35 U.S.C. 112, second paragraph. Thus, in the instant rejection, the phrase is being interpreted as cells which exhibit similar properties as that of human stem cells. Tsukamoto *et al.* teach the production of human hematopoietic stem cell capable of producing members of each of the hematopoietic lineages, that is differentiated cells (see abstract and claims 1 and 2). Thus, without a distinction indicating a structural or functional difference of the claimed cells, the human hematopoietic cells and differentiated cells produced therefrom taught by Tsukamoto *et al.* meet all of the limitations of the claimed cells.

Accordingly, Tsukamoto *et al.* clearly anticipate the claimed invention.

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Claims 27-34 and 50-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamane (Japanese Journal of Cancer and Chemotherapy, 1987).

Note that the same product-by-process analysis is applied here as in the preceding rejections. The claims are not clearly defined (112/2nd) or enabled (112/1), thus, the phrase "human embryonic or stem-like cells" is not distinguishable over human differentiated cells.

Yamane disclose human differentiated cells derived from epithelial cells, skin keratinocytes and endothelial cells (see summary in abstract). Thus, without any distinction indicating a structural or functional difference of the claimed cells, the human differentiated cells of Yamane meet all of the limitations of the claimed cells.

Accordingly, Yamane clearly anticipates the claimed invention.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-36 and 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsukamoto *et al.* (US Patent 5,716,827).

Claims 35 and 36 are directed to human differentiated cells which contain and express an inserted gene. Tsukamoto *et al.* disclose recombination techniques known in the prior art for insertion of a gene of interest into mammalian cells. See column 8, lines 9-11. Accordingly, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify differentiated human cells produced by stem cell precursors to comprise a gene of interest with a reasonable expectation of success.

Thus, the claimed invention, as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-34 and 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe *et al.* (Theriogenology, 1990), Collas *et al.* (Molecular Reproduction and Development, 1994) and Westhusian *et al.* (Theriogenology, 1996).

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The claims are directed to a method of producing human embryonic or stem-like cells via nuclear transfer of a differentiated human or mammalian cell nucleus to an animal oocyte. See 112, second paragraph, rejection with regard to the indefiniteness of the limitation 'embryonic or stem-like cells'. It is unclear what cells result from the culture of NT units in the absence of a showing of unexpected results by Applicants relating to the production of true ES cells or differentiation capacity of the ES-like cells of the invention. As such, the cited prior art is interpreted to provide sufficient motivation to select cross-species differentiated mammalian cell nuclei and oocytes for use in nuclear transfer methodology with a reasonable expectation of producing at least one nuclear transfer unit of which is capable of being cultured into any type of cell which meets the limitations of "embryonic or stem-like" cell.

Wolfe *et al.* teach a method of cross-species nuclear transfer using nuclei from bovine preimplantation embryos and oocytes of a varying species. Wolfe *et al.* disclose the production of blastocyst derived from bovine nuclei and bison ovum as well as bovine nuclei and goat ovum. Thus, the experimentation of Wolfe *et al.* demonstrates that mammalian nuclei may be capable of interacting with cytoplasm from other mammalian species to support normal development (see summary in Abstract). Wolfe *et al.* do not propose nuclear transfer of human or mammalian differentiated nuclei into bovine oocytes, however, at the time the claimed invention was made, Collas *et al.* disclose results indicating that transplanted differentiated nuclei may be pluripotent.

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Collas *et al.* also suggest that "a variety of differentiated mammalian cell types may promote early preimplantation development of NT embryos." (page 266, Discussion section). Accordingly, in view of the collective cited prior art, it would have been *prima facie* obvious for one of ordinary skill in the art to select human or mammalian differentiated cell nuclei and animal oocytes of a varying species for use in nuclear transfer with a reasonable expectation of producing at least one nuclear transfer unit of which is capable of being cultured into cells which meet the limitation of "embryonic or stem-like" cells.

Further, at the time of the claimed invention, it was recognized that the various methods for nuclear transfer had technical drawbacks which reduced the efficiency of the methodology. Westhusin *et al.* teach that one such limitation occurs during the process of enucleating the oocyte when ovum cytoplasm is removed (page 244; fourth column). Further, Westhusin *et al.* note that their experiments and those of others clearly indicate that the cytoplasm/nuclear ratio plays an important role in embryonic development, where reduced levels of cytoplasm results in a significant effect on embryo survival (page 244; first column). In view of their results and that reported by others, Westhusin *et al.* conclude that a reduction in the amount of cytoplasm affects the number of cells in the morula and blastocyst, affects embryo quality, and may affect later embryo development (page 248; beginning of discussion section). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the

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art at the time the invention was made to control the amount of cytoplasm during the procedure of nuclear transfer. As noted by Westhusin *et al.* many of the nuclear transfer procedures result in the loss of cytoplasm, so one of ordinary skill in the art would have been motivated, in view to the work of Westhusin *et al.* to include the addition of cytoplasm to the NT unit. In addition, it is also noted that the cytoplasm/nuclear ratio is an important factor in the survivability of the embryo, thus, the artisan would have been further motivated to control the cytoplasm/nuclear ratio by the addition of cytoplasm during the nuclear transfer procedure which was lost during enucleation.

There would have been a reasonable expectation of success given the state of art and the ability to perform nuclear transfer procedures at the time of the claimed invention. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. *In re O'Farrell* 7USPQ2d 1673 (CAFC 1988).

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Takeda *et al.* Journal of Reproduction and Fertility 116:253-259, 1999.

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***Conclusion***

No claim is allowed. Claims 35-49 appear to be free of the art of record because the art fails to teach cross-species nuclear transplantation to obtain donor cells which are genetically modified and useful as embryonic stem cells. However, these claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732.

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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